PATENT SPECIFICATION (11) 1375836

1375836

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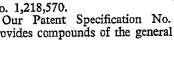
(54) INDOLES

(71) We, JOHN WYETH & BROTHER LIMITED, a British company of Huntercombe Lane South, Taplow, Maidenhead, Berkshire, do hereby declare the invention for which we pray that a patent may be granted to us and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention relates to a process for the preparation of indole derivatives and pharmaceutical compositions containing compounds prepared thereby, and is an improvement in or modification of our Patent Specification No. 1,218,570.

Our Patent Specification No. 1,218,570 provides compounds of the general formula



(I)

in which formula

represents a ring system of the general formula

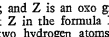
(IIa)

(IIb) (IIc)

R^1 represents hydrogen, lower alkyl, lower aralkyl or aroyl; R^2 represents hydrogen, lower alkyl or aryl; R^3 represents hydrogen, halogen, lower alkoxy, hydroxy or lower alkyl; R^4 represents hydrogen, halogen or lower alkyl; R^5 represents aryl (including heteroaryl), lower alkoxy, aryloxy, lower aralkyl, lower aralkyloxy or diaryl-lower alkyl; $X^\ominus$ is an anion; A represents an alkylene or mono- or di-keto alkylene radical containing up to 4 carbon atoms; and Z is an oxo group with the proviso that Z in the formula II(c) may also represent two hydrogen atoms when A is alkylene and R^5 is aryl, the terms "lower alkyl" and "lower alkoxy" mean the radical contains 1 to 6 carbon atoms and the term "lower aralkyl" means the radical contains 7 to 10 carbon atoms.

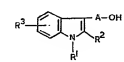
Furthermore, the same Patent Specification provides processes for the preparation of said compounds, which consist in building up the molecule from suitable starting materials in known manner. Further details of the specific processes can be obtained by reference to Patent Specification No. 1,218,570.

We have now found that the compounds of general formula (I) in which

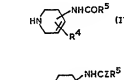


represents a ring system of formula (IIb) or (IIc), R^1, R^2, R^3, R^4 and Z have the meanings defined in connection with formulae (I), (IIb) or (IIc), A is an alkylene radical containing

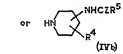
up to 4 carbon atoms, and R^5 represents aryl (including heteroaryl), lower alkoxy, aryloxy, lower aralkyl, lower aralkyloxy, diaryl-lower alkyl or a cycloalkyl radical containing 5 to 7 carbon atoms, can be prepared by reaction of a compound of the general formula


(III)

(in which R^1, R^2, R^3 and A have the meanings defined immediately above) with a compound of formula


(IVa)

or


(IVb)

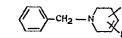
(in which R^4, R^5 and Z have the meanings defined immediately above).

The reaction is carried out in the presence of a catalyst. Preferably the catalyst is a nickel catalyst, for example Raney nickel. An organic solvent, which is inert under the reaction conditions, is usually used for example xylene, toluene or benzene. Preferably the reaction is carried out by heating the reactants under reflux in a water immiscible organic solvent, for example xylene, and removing the water formed during the reaction by azeotropic distillation. If necessary, reactive substituent groups can be blocked during a reaction and released later.

The starting materials of general formula (IVa) and (IVb) can be prepared by those methods outlined in Patent Specification No. 1,218,570 and in co-pending Application No. 35231/68 (Serial No. 1,273,563). In particular, to prepare a compound of formula (IVb), an aminopyridine of formula


(V)

is acylated with a reactive derivative of an acid of general formula $R^5.COOH$, quaternised with a benzyl halide, for example benzyl chloride, and then subjected to reduction with an alkali metal borohydride, for example sodium or potassium borohydride to give the N - benzyl - tetrahydropyridine of formula


(VI)

This tetrahydropyridine is then further reduced, for example by catalytic hydrogenation, to give the piperidine of formula (IVb).

The starting materials of general formula (III) are either known compounds or may be prepared by methods known for making compounds of this type.

Once a tetrahydropyridine compound of general formula (I) [in which

represents a ring system of formula (IIb), R^1, R^2, R^3, R^4 and Z have the meanings defined in connection with formula (I) or (IIb), A is an alkylene radical containing up to 4 carbon atoms and R^5 represents aryl (including heteroaryl), lower alkoxy, aryloxy, lower aralkyl, lower aralkyloxy, diaryl-lower alkyl or a cycloalkyl radical containing 5 to 7 carbon atoms] has been prepared, it may be reduced to the corresponding piperidine in which

represents a ring system of formula (IIc).

Once a compound of general formula (I) [in which

represents a ring system of formula (IIb) or (IIc), R^2, R^3, R^4 and Z have the meanings defined in connection with formula (I), (IIb) or (IIc), A is an alkylene radical containing up to 4 carbon atoms and R^5 represents aryl (including heteroaryl), lower alkoxy, aryloxy, lower aralkyl, lower aralkyloxy, diaryl-lower alkyl or a cycloalkyl radical containing 5 to 7 carbon atoms and R^1 is a hydrogen atom] has been prepared, derivatives thereof may be prepared by alkylation, aralkylation or aroylation at the 1-position. For example, an alkali metal salt (e.g. the sodium salt) can be prepared and reacted with an alkyl or aralkyl halide or with an aroylating agent.

As a further aspect of the invention, there is provided the compounds of general formula (I) in which

represents a ring system of formula (IIb) or (IIc), R^1, R^2, R^3, R^4 and Z have the meanings defined in connection with formula (I), (IIb) or (IIc), A is an alkylene radical containing up to 4 carbon atoms and R^5 represents aryl (including heteroaryl), lower alkoxy, aryloxy, lower aralkyl, lower aralkyloxy, diaryl-lower alkyl or a cycloalkyl radical containing 5 to 7 carbon atoms, when prepared by the process of the invention.

The groups R^1, R^2, R^3, R^4 and R^5 may be the same as those mentioned in Patent Specification No. 1,218,570 or our co-pending Application No. 3523/68. Examples of R^1 are hydrogen, methyl, ethyl, *n* - propyl, isopropyl, *n* - butyl, isobutyl, benzyl, benzoyl and *p* - chlorobenzoyl. Preferably R^1 is a hydrogen atom. R^2 can be, for example, hydrogen, methyl, ethyl, *n* - propyl, isopropyl, *n* - butyl, isobutyl or substituted or unsubstituted phenyl, and is preferably hydrogen or methyl. R^3 can be, for example, hydrogen, chlorine, methoxy, ethoxy, hydroxy, methyl, ethyl, *n* - propyl, isopropyl, *n* - butyl or isobutyl. Preferably R^3 is a hydrogen atom. Examples of R^4 are hydrogen, chlorine, methyl, ethyl, *n* - propyl, isopropyl, *n* - butyl or isobutyl, though preferably R^4 is a hydrogen atom. R^5 can be, for example, phenyl, substituted phenyl, (e.g. phenyl substituted by halogen such as chlorine, by alkoxy, such as methoxy or ethoxy, by alkyl such as methyl or ethyl or by methylenedioxy), heterocyclic radicals (such as 3 - indolyl, 2 - thienyl or 2 - furyl), methoxy, ethoxy, phenoxy, benzyl, benzyloxy, diphenylmethyl and cyclohexyl.

Since the compounds prepared by the process of the invention contain a basic nitrogen atom, they can form acid addition salts with acids (for example, hydrochloric acid) or quaternary ammonium salts, for example with alkyl halides (for example, methyl chloride or bromide), and the invention also provides such salts of the compounds prepared by the process of the invention.

The compounds prepared by the process of the invention have pharmacological properties or are useful as intermediates for the preparation of compounds having pharmacological properties. The compounds generally exhibit anti-inflammatory activity and/or action on the cardiovascular system (such as hypotensive and/or anti-hypertensive activity) and/or anti-histamine activity and sometimes central nervous system activity (such as sedative or anti-convulsant activities) when tested on warm blooded animals.

The invention also includes a pharmaceutical composition comprising a compound of the general formula (I) in which

represents a ring system of formula (IIb) or (IIc), R^1, R^2, R^3, R^4 and Z have the meanings defined in connection with formula (I), (IIb), or (IIc), A is an alkylene radical containing up to 4 carbon atoms and R^5 represents aryl (including heteroaryl), lower alkoxy, aryloxy, lower aralkyl, lower aralkyloxy, diaryl-lower alkyl or a cycloalkyl radical containing 5 to 7 carbon atoms, or an acid addition or quaternary ammonium salt thereof, when prepared according to the process of the invention and which may be micronised, in association with a pharmaceutically acceptable carrier. Any suitable carrier known in the art can be used to prepare the pharmaceutical compositions. Carriers are discussed in more detail in our Patent Specification 1,128,570.

The following Examples 1, 11, 12, 13 and 14 illustrate the invention; Examples 2 to 10 concern the preparation of intermediates and/or starting materials:

EXAMPLE 1

3 - [2 - (4 - Benzamido - 1 - piperidyl)-ethyl]indole

Tryptophol (1.61 g., 0.01 mole), 4 - benzamidopiperidine (2.04 g., 0.01 mole) and Raney nickel (W2, *ca* 2 g.) were suspended in xylene (150 ml.) and the stirred mixture boiled under reflux for 5 hours. Liberated water was removed by means of a Dean and Stark apparatus. Filtration of the *hot*-mixture provided a yellow solution which was stored at room temperature until crystallisation was complete (about 16 hours). The title compound was obtained as buff-coloured needles (2.49 g.), m.p. 194.2°C.

EXAMPLE 2

4 - Amino - 1 - benzylpiperidine dihydrochloride, monohydrate

A solution of 4 - benzamido - 1 - benzylpiperidine (5.89 g.) in hydrochloric acid (65.5 ml. of concentrated acid diluted to 120 ml.) was refluxed for 24 hours. After having cooled to ambient temperature the reaction mixture was extracted with chloroform (3×100 ml.).

The aqueous acid phase was strongly basified with solid potassium carbonate and then extracted with chloroform (3×100 ml.). The organic extracts were evaporated to dryness and the oil obtained dissolved in benzene (100 ml.). After filtration, hydrogen chloride gas was passed through the solution until precipitation was complete. After standing for 24 hours at 4°C., the product (4.37 g.) was collected, washed with fresh solvent and dried.

EXAMPLE 3

1 - Benzyl - 4 - cyclohexanecarboxamidopiperidine

To a solution of 4 - amino - 1 - benzylpiperidine dihydrochloride, monohydrate

(0.703 g.) in water (5 ml.) was added anhydrous potassium carbonate (1.73 g.) and chloroform (12.5 ml.). After swirling for a few minutes a solution of cyclohexanecarbonyl chloride (0.367 g.) in chloroform (2.5 ml.), was added.

After stirring for 24 hours, the aqueous phase was extracted with chloroform (3×25 ml.). The organic extracts were evaporated to dryness, and the solid so obtained recrystallised from ethyl acetate to give the product (0.508 g.), m.p. 158.3°C. (Found:— C, 75.6; H, 9.4; N, 9.2. $C_{19}H_{28}N_2O$ requires C, 75.9; H, 9.4; N, 9.2%).

EXAMPLE 4

4 - Cyclohexanecarboxamidopiperidine

A mixture of 1 - benzyl - 4 - cyclohexanecarboxamidopiperidine (0.6 g.) and palladium-charcoal catalyst (5%; 0.6 g.) in glacial acetic acid (0.2 ml.) and methanol (30 ml.) was hydrogenated at 50°C. and 50 p.s.i.

The mixture was filtered through kieselguhr and the filtrate evaporated to dryness. The residual oil was dissolved in water (10 ml.) sodium hydroxide solution (15 ml; 10 M) added, and the solution extracted with chloroform (3×25 ml.). The organic extracts were evaporated to dryness, and the solid obtained recrystallised from water to give the product (0.17 g.), m.p. 179.2°C. (Found:— C, 68.85; H, 10.6; N, 13.4. $C_{12}H_{22}O$ requires C, 68.5; H, 10.5; N, 13.3%).

EXAMPLE 5

1 - Benzyl - 4 - (3,4 - methylenedioxybenzamido)piperidine

Prepared in a similar manner to the compound of Example 3 but using piperonyl chloride in place of cyclohexanecarbonyl chloride. The title compound crystallised from isopropanol, m.p. 165.3°C. (Found:— C, 71.1; H, 6.8; N, 8.4. $C_{20}H_{22}N_2O_3$ requires C, 71.0; H, 6.55; N, 8.3%).

EXAMPLE 6

4 - (3,4 - Methylenedioxybenzamido)-piperidine

Prepared in a similar manner to the compound of Example 4 but using the product of Example 5 in place of that of Example 3. The title compound crystallised from acetonitrile, m.p. 160.2°C. (Found:— C, 63.1; H, 6.6; N, 11.2; $C_{13}H_{16}N_2O_3$ requires C, 62.9; H, 6.5; N, 11.3).

EXAMPLE 7

1 - Benzyl - 4 - (3 - methoxybenzamido)-piperidine

Prepared in a similar manner to the compound of Example 3 but using 3 - methoxybenzoyl chloride in place of cyclohexanecarbonyl chloride. The title compound recrystallised from isopropanol, m.p. 153.6°C. (Found:— C, 74.3; H, 7.4; N, 8.45. $C_{20}H_{22}N_2O_2$ requires C, 74.05; H, 7.5; N, 8.6%).

EXAMPLE 8

4 - (3 - Methoxybenzamido)piperidine

Prepared in a similar manner to the compound of Example 4 and using the product of Example 7 in place of that of Example 3. The title compound crystallised from water, m.p. 111.3°C (Dec). (Found:— C, 65.5; H, 8.1; N, 11.5. $C_{13}H_{18}N_2O_2 . 1/4\,H_2O$ requires C, 65.4; H, 7.8; N, 11.7%).

EXAMPLE 9

1 - Benzyl - 4 - (4 - methylbenzamido)-piperidine

Prepared in a similar manner to the compound of Example 3 but using 4 - tolyl chloride in place of cyclohexanecarbonyl chloride. The title compound crystallised from isopropanol, m.p. 160.6°C. (Found:— C, 78.2; H, 7.9; N, 8.8. $C_{20}H_{24}N_2O$ requires C, 77.9; H, 7.8; N, 9.1%).

EXAMPLE 10

4 - (4 - Methylbenzamido)piperidine

Prepared in a similar manner to the compound of Example 4 but using the product of Example 9 in place of that of Example 3. The title compound crystallised from water, m.p. 182.2°C. (Found:— C, 72.45; H, 8.5; N, 12.6. $C_{13}H_{18}N_2O$ requires C, 71.5; H, 8.3; N, 12.8%).

EXAMPLE 11

3 - [2 - (4 - [p - Methylbenzamido] - 1 - piperidyl)ethyl]indole

Tryptophol (0.81 g., 0.005 mole), 4 - (p - methylbenzamido)piperidine (1.09 g., 0.005 mole) and Raney nickel (W2; *ca* 1 g.) were suspended in xylene (75 ml.) and the stirred mixture boiled under reflux for 5 hours. Liberated water was removed by means of a Dean and Stark apparatus. Filtration of the hot mixture afforded a yellow solution which was stored at room temperature until crystallisation was complete (about 16 hours). The title compound was obtained as needles, m.p. 200—202°C.

EXAMPLE 12

3 - [2 - (4 - [3 - Methoxybenzamido] - 1 - piperidyl)ethyl]indole

Tryptophol (0.81 g., 0.005 mole) and 4-(3-methoxybenzamido)piperidine (1.17 g., 0.005 mole) were condensed in the presence of Raney nickel (W2, *ca.* 1g.) following the method of Example 11 to give the title compound, m.p. 152—4°C.

EXAMPLE 13

3 - [2 - (4 - [3,4 - Methylenedioxybenzamido] - 1 - piperidyl)ethyl]indole

Tryptophol (0.81 g., 0.005 mole) and 4 - (3,4 - methylenedioxy)benzamidopiperidine

(1.2 g., 0.005 mole) were condensed in the presence of Raney nickel (W2, *ca.* 1 g.) following the method of Example 11 to give the title compound, m.p. 189—190°C.

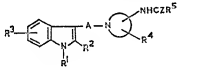
EXAMPLE 14

3 - [2 - (4 - [Cyclohexanecarboxamido] - 1 - piperidyl)ethyl]indole

Tryptophol (0.81 g., 0.005 mole) and 4 - cyclohexanecarboxamidopiperidine (1.05 g., 0.005 mole) were condensed in the presence of Raney nickel (W2, *ca.* 1 g.) following the method of Example 11 to give the title compound, m.p. 182—4°C.

WHAT WE CLAIM IS:—

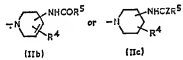
1. A process for the preparation of a compound of the general formula



(I)

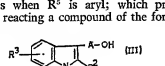
in which formula

represents a ring system of the general formula



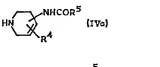
(IIb) (IIc)

R^1 represents hydrogen, lower alkyl, lower aralkyl or aroyl; R^2 represents hydrogen, lower alkyl or aryl, R^3 represents hydrogen, halogen, lower alkoxy, hydroxy or lower alkyl; R^4 represents hydrogen, halogen or lower alkyl; R^5 represents aryl (including heteroaryl), lower alkoxy, aryloxy, lower aralkyl, lower aralkyloxy, diaryl-lower alkyl or a cycloalkyl radical containing 5 to 7 carbon atoms; A represents an alkylene radical containing up to 4 carbon atoms; and Z is an oxo group with the proviso that Z in the formula II(c) may also represent two hydrogen atoms when R^5 is aryl; which process comprises reacting a compound of the formula



(III)

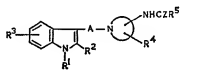
(in which R^1, R^2, R^3 and A have the meanings defined immediately above) with a compound of formula



(IVa) (IVb)

(in which R^4, R^5, and Z have the meanings defined immediately above), in the presence of a catalyst.

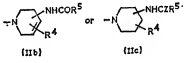
2. A process for the preparation of a compound of the general formula



(I)

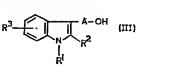
in which formula

represents a ring system of the general formula



(IIb) (IIc)

R^1 represents hydrogen, lower alkyl, lower aralkyl or aroyl; R^2 represents hydrogen, lower alkyl or aryl; R^3 represents hydrogen, halogen, lower alkoxy, hydroxy or lower alkyl; R^4 represents hydrogen, halogen or lower alkyl; R^5 represents aryl (including heteroaryl), lower alkoxy, aryloxy, lower aralkyl, lower aralkyloxy or diaryl-lower alkyl radical; A represents an alkylene radical containing up to 4 carbon atoms; and Z is an oxo group with the proviso that Z in the formula II(c) may also represent two hydrogen atoms when R^5 is aryl; which process comprises reacting a compound of the formula



(III)

(in which R^1, R^2, R^3 and A have the meanings defined immediately above) with a compound of formula


(IVa)


(IVb)

(in which R^1, R^2 and Z have the meanings defined immediately above), in the presence of a catalyst.

3. A process according to Claim 1, in which the catalyst is a nickel catalyst.

4. A process according to Claim 3, in which the nickel catalyst is Raney nickel.

5. A process according to any one of Claims 1, 3 and 4, in which the compound of formula (III) is reacted with one of formula (IVa).

6. A process according to any one of Claims 1, 3 and 4, in which the compound of formula (III) is reacted with one of formula (IVb).

7. A process according to Claim 5, in which the compound produced of formula (I) in which

represents a ring system of formula (IIb) is reduced to the corresponding compound in which

represents a ring system of formula (IIc).

8. A process according to any one of Claims 1 and 3 to 7, in which R^1 in the compound of formula (I) produced is a hydrogen atom and that this compound is alkylated, aralkylated or aroylated to introduce a group R^1 as defined in Claim 1 and other than hydrogen.

9. A process according to any one of Claims 1 and 3 to 8, in which R^1 is methyl, ethyl, *n* - propyl, *iso* - propyl, *n* - butyl, *iso* - butyl, benzyl, benzoyl, and *p* - chlorobenzoyl.

10. A process according to any one of Claims 1 and 3 to 7, in which R^1 is hydrogen.

11. A process according to any one of Claims 1 and 3 to 10, in which R^2 is methyl, ethyl, *n* - propyl, *iso* - propyl, *n* - butyl, *iso* - butyl or substituted or unsubstituted phenyl.

12. A process according to any one of Claims 1 and 3 to 10, in which R^2 is hydrogen.

13. A process according to any one of Claims 1 and 3 to 12, in which R^3 is chlorine, methoxy, ethoxy, hydroxy, methyl, ethyl, *n* - propyl, *iso* - propyl, *n* - butyl or *iso* - butyl.

14. A process according to any one of Claims 1 and 3 to 12, in which R^3 is a hydrogen atom.

15. A process according to any one of Claims 1 and 3 to 14, in which R^4 is chlorine, methyl, ethyl, *n* - propyl, *iso* - propyl, *n* - butyl or *iso* - butyl.

16. A process according to any one of Claims 1 and 3 to 14, in which R^4 is hydrogen.

17. A process according to any one of Claims 1 and 3 to 16, in which R^5 is halophenyl, alkoxyphenyl, alkylphenyl, methylenedioxyphenyl, indol - 3 - yl, thien - 2 - yl, fur - 2 - yl, methoxy, ethoxy, phenoxy, benzyl, benzyloxy, diphenylmethyl or cyclohexyl.

18. A process according to any one of Claims 1 and 3 to 16, in which R^5 is 3,4 - methylenedioxyphenyl, 4 - methylphenyl, 3 - methoxyphenyl or cyclohexyl.

19. A process according to any one of Claims 1 and 3 to 18, in which A is ethyl.

20. A process according to any one of Claims 1 and 3 to 19, in which the group —NHCZR^2 is at the 4-position of the piperidine or tetrahydropyridine ring.

21. A process according to any one of Claims 1, 3, 4 and 6 to 20, in which Z is an oxo group.

22. A process in which tryptophol is reacted with 4 - (*p* - methylbenzamido)piperidine in the presence of Raney nickel and the product is 3 - [2 - (4 - [*p* - methylbenzamido] - 1 - piperidyl)ethyl]indole.

23. A process in which tryptophol is reacted with 4 - (3 - methoxybenzamido)piperidine in the presence of Raney nickel and the product is 3 - [2 - (4 - [3 - methoxybenzamido] - 1 - piperidyl)ethyl]indole.

24. A process in which tryptophol is reacted with 4 - (3,4 - methylenedioxybenzamido)-piperidine in the presence of Raney nickel and the product is 3 - [2 - (4 - [3,4 - methylenedioxybenzamido] - 1 - piperidyl)ethyl]indole.

25. A process in which tryptophol is reacted with 4 - cyclohexanecarboxamidopiperidine in the presence of Raney nickel and the product is 3 - [2 - (4 - cyclohexanecarboxamido - 1 - piperidyl)ethyl]indole.

26. A process as claimed in any of Claims 1, 3, 4, 6, 10, 12, 14 and 16 to 25, substantially as described herein and shown with reference to any of Examples 11 to 14.

27. Indoles when prepared by the process claimed in any of Claims 1 and 3 to 26.

28. A pharmaceutical composition comprising a compound as claimed in Claim 27 and a pharmaceutically acceptable carrier.

29. A process according to Claim 2, in which the catalyst is a nickel catalyst.

30. A process according to Claim 29, in which the nickel catalyst is Raney nickel.

31. A process according to any one of Claims 2, 29 and 30 in which the compound of formula (III) is reacted with one of formula (IVa).

32. A process according to any one of Claims 2, 29 and 30, in which the compound of formula (III) is reacted with one of formula (IVb).

33. A process according to Claim 31, in which the compound produced of formula (I) in which

represents a ring system of formula (IIb) is reduced to the corresponding compound in which

represents a ring system of formula (IIc).

34. A process according to any one of Claims 2 and 29 to 33, in which R^1 in the compound of formula (I) produced is a hydrogen atom and that this compound is alkylated, aralkylated or aroylated to introduce a group R^1 as defined in Claim 2 and which is other than hydrogen.

35. A process according to any one of Claims 2 and 29 to 34, in which R^1 is methyl, ethyl, *n* - propyl, *iso* - propyl, *n* - butyl, *iso* - butyl, benzyl, benzoyl and *p* - chlorobenzoyl.

36. A process according to any one of Claims 2 and 29 to 33, in which R^1 is hydrogen.

37. A process according to any one of Claims 2 and 29 to 36, in which R^2 is methyl, ethyl, *n* - propyl, *iso* - propyl, *n* - butyl, *iso* - butyl or substituted or unsubstituted phenyl.

38. A process according to any one of Claims 2 and 29 to 36, in which R^2 is hydrogen.

39. A process according to any one of Claims 2 and 29 to 38, in which R^3 is chlorine, methoxy, ethoxy, hydroxy, methyl, ethyl, *n* - propyl, *iso* - propyl, *n* - butyl or *iso* - butyl.

40. A process according to any one of Claims 2 and 29 to 38, in which R^4 is a hydrogen atom.

41. A process according to any one of Claims 2 and 29 to 40, in which R^4 is chlorine, methyl, ethyl, *n* - propyl, *iso* - propyl, *n* - butyl or *iso* - butyl.

42. A process according to any one of Claims 2 and 29 to 40, in which R^4 is hydrogen.

43. A process according to any one of Claims 2 and 29 to 42, in which R^5 is halophenyl, alkoxyphenyl, alkylphenyl, methylenedioxyphenyl, indol - 3 - yl, thien - 2 - yl, fur - 2 - yl, methoxy, ethoxy, phenoxy, benzyl, benzyloxy or diphenylmethyl.

44. A process according to any one of Claims 2 and 29 to 42, in which R^5 is phenyl.

45. A process according to any one of Claims 2 and 29 to 44, in which A is ethyl.

46. A process according to any one of Claims 2 and 29 to 45, in which the group —NHCZR^5 is at the 4-position of the piperidine or tetrahydropyridine ring.

47. A process according to any one of Claims 2, 29, 30 and 32 to 46, in which Z is an oxo group.

48. A process in which tryptophol is reacted with 4 - benzamidopiperidine in the presence of Raney nickel and the product is 3 - [2 - (4 - benzamido - 1 - piperidyl)ethyl]indole.

49. A process as claimed in any of Claims 2, 29, 30, 32, 36, 38, 40, 42, and 44 to 48, substantially as described herein and shown with reference to Example 1.

50. Indoles when prepared by the process claimed in any of Claims 2 and 29 to 49.

51. A pharmaceutical composition comprising a compound as claimed in Claim 50, and a pharmaceutically acceptable carrier.

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